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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

| | | |
|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Applicant's or agent's file reference WO 550 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP03/50080 | International filing date (day/month/year) 26/03/2003 | Priority date (day/month/year) 10/04/2002 |
| International Patent Classification (IPC) or national classification and IPC A61K38/17 | | |
| Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Date of submission of the demand 07/11/2003 | Date of completion of this report 18/02/2004 |
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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

INTERNATIONAL SEARCH REPORT

In Application No
PCT/03/50080

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/17 A61K48/00 A61K38/21 A61P37/00 A61P29/00
//(A61K38/17,31:65),(A61K38/17,31:505),(A61K38/21,38:17)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| X | WO 99 53942 A (AMGEN INC) 28 October 1999 (1999-10-28) | 1,2, 4-11, 13-18 |
| Y | page 2, line 24 -page 4, line 21 page 6, line 20-30 page 8, line 27 -page 9, line 26 page 10, line 15-34 page 12, line 28-36 page 13, line 17-25 page 20, line 32 -page 21, line 12 page 24, line 16 page 25, line 13-19 --- -/-- | 1-25 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 October 2003

Date of mailing of the international search report

17/10/2003

Name and mailing address of the ISA

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Authorized officer

Lechner, 0

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Y | <p>BUCAI NATHAN ET AL: "Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification" GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, US, vol. 12, no. 9, 1 May 1998 (1998-05-01), pages 1260-1268, XP002210981 ISSN: 0890-9369 abstract page 1260, right-hand column, paragraph 3 -page 1261, left-hand column, paragraph 1 page 1265, right-hand column, last paragraph page 1266, right-hand column, last paragraph</p> | 1-25 |
| Y | <p>WIGLEY F M ET AL: "NOVEL THERAPY IN THE TREATMENT OF SCLERODERMA" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 1, no. 10, 2001, pages 31-48, XP001062098 ISSN: 1354-3784 cited in the application abstract</p> | 1-25 |
| Y | <p>WO 98 35043 A (GENETICS INST) 13 August 1998 (1998-08-13) page 20, line 15-17, 24, 25, 30, 31</p> | 24, 25 |
| P, Y | <p>WO 02 46225 A (PLATER ZYBERK CHRISTINE ;COLINGE JACQUES (FR); POWER CHRISTINE (FR) 13 June 2002 (2002-06-13) the whole document</p> | 24, 25 |
| A | <p>HERON EMMANUEL ET AL: "Intracerebral calcification in systemic sclerosis" STROKE, AMERICAN HEART ASSOCIATION, DALLAS TX, US, vol. 30, no. 10, October 1999 (1999-10), pages 2183-2185, XP002210982 ISSN: 0039-2499 abstract</p> | 1-25 |
| | <p>---</p> <p>-/--</p> | |

INTERNATIONAL SEARCH REPORT

International Application No.

EP 03/50080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A | <p>YANO K ET AL: "Synovial cells from a patient with rheumatoid arthritis produce osteoclastogenesis inhibitory factor/osteoprotegerin: reciprocal regulation of the production by inflammatory cytokines and basic fibroblast growth factor" JOURNAL OF BONE AND MINERAL METABOLISM, SPRINGER, TOKYO, JP, vol. 19, no. 6, 2001, pages 365-372, XP002210983 ISSN: 0914-8779 abstract figure 5 page 370, right-hand column, last paragraph -page 371, right-hand column, paragraph 1</p> <p>----</p> | 1-25 |
| A | <p>CLARK-EA ET AL: "Osteoprotegerin is an alphavbeta3-induced, NF-kappaB-dependent survival factor for endothelial cells" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 275, no. 28, 14 July 2000 (2000-07-14), pages 20959-20962, XP002210984 ISSN: 0021-9258 abstract</p> <p>-----</p> | 1-25 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50080

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 25 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-25 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-25 (all partially)

Present claims 1-25 relate to an extremely large number of possible molecules, defined as having 40-80% homology of SeqID No 2 or 4 or a polypeptide having 1, 2, 3 or 4 cysteine-rich domains of osteoprotegerin, a mutein which hybridizes under moderately stringent conditions, functional derivatives, active fractions or circularly permuted derivatives of any of (a) to (g), isoforms, fused protein of active fraction of any of (a) to (g), expression vector sequence, a gene therapy vector sequence. In fact, the claims contain so many options that a lack of clarity (and conciseness) within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the molecules disclosed in claims 1 and 10 points (a), (b), (c) as far as relating to four cysteine-rich domains, (d) and (e) as far as relating to 90% identity.

Claims 21, 23, 24 relate to molecules defined by reference to a desirable characteristic or property, i.e. e.g. TNF antagonist, anti-scleroderma-agent, ACE inhibitor, calcium channel blockers, proton pump inhibitors, NSAIDs, COX-inhibitors, geranylgeranyl transferase inhibitors, prolyl-4-hydroxylase inhibitors, c-proteinase inhibitors, lysyl-oxidase inhibitors, angiotensin II inhibitors, or anti-oxidants. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such molecules. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the molecules by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to interferon(-beta), TBP1, TBP2, halofuginone, tetracycline, pentoxifylline, bucillamine, rotterlin, corticosteroids, relaxin, endothelin-1 and NO.

Finally, claims 1-2, 4-11 and 13-25 relate to an extremely large number of ill defined pathologic conditions/diseases circumscribed by a patho-physiological or -anatomical mechanism, i.e. fibrotic disease, connective tissue disease. Support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the diseases claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to fibrosis/sclerosis and scleroderma.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 03/50080

| Patent document cited in search report | | Publication date | Patent-family member(s) | Publication date |
|-------------------------------------------|---|---------------------|----------------------------|---------------------|
| WO 9953942 | A | 28-10-1999 | AU 757806 B2 | 06-03-2003 |
| | | | AU 3660599 A | 08-11-1999 |
| | | | CA 2325360 A1 | 28-10-1999 |
| | | | EP 1073456 A1 | 07-02-2001 |
| | | | JP 2002512199 T | 23-04-2002 |
| | | | WO 9953942 A1 | 28-10-1999 |
| WO 9835043 | A | 13-08-1998 | AU 4899397 A | 26-08-1998 |
| | | | EP 0954580 A1 | 10-11-1999 |
| | | | JP 2001511010 T | 07-08-2001 |
| | | | WO 9835043 A1 | 13-08-1998 |
| | | | US 2003175855 A1 | 18-09-2003 |
| WO 0246225 | A | 13-06-2002 | AU 2636602 A | 18-06-2002 |
| | | | CA 2428092 A1 | 13-06-2002 |
| | | | CZ 20031855 A3 | 17-09-2003 |
| | | | EE 200300213 A | 15-08-2003 |
| | | | WO 0246225 A2 | 13-06-2002 |
| | | | NO 20032597 A | 06-06-2003 |